K013148 FEB 2 8 2002

SUMMARY OF SAFETY AND EFFECTIVENESS INFORMATION

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR § 807.92.

GENERAL INFORMATION:

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Date of Preparation: January 30, 2002

Device Generic Name: Mouse Monoclonal Anti-Estrogen Receptor Antibody

Device Trade Name: BioGenex Mouse Monoclonal Anti-Estrogen Receptor Antibody (Clone ER88)

Device Classification Name: Immunohistochemistry Reagents and Kits

Assigned 510(k) Number: K013148

PREDICATE DEVICE:

The device is substantially equivalent to certain well-established, widely accepted reference laboratory methodology dextran-coated charcoal (DCC) technique which were common in use prior to May 28, 1976. The device is substantially equivalent in methodology to similar kit for estrogen receptor (Dako, K993957).

DESCRIPTION OF THE DEVICE:

BioGenex ER88 is a monoclonal antibody, which specifically binds to estrogen receptor antigen located in the nuclear region of a variety of normal and abnormal tissues. It is a mouse monoclonal anti-estrogen receptor antibody from mouse ascites fluid diluted in phosphate buffered saline pH 7.6 containing bovine serum albumin as carrier protein and 0.09% sodium azide as preservative. The antibody is available in concentrated (MU368-UC) as well as ready to use form (AM368-5M and AM368-10M). Refer to package insert for details.

INTENDED USE:

The BioGenex Mouse Monoclonal Anti-Estrogen Receptor Antibody (Clone ER88) is an immunohistochemical (IHC) assay and is intended for laboratory use to qualitatively identify by light microscopy human estrogen receptor in normal and/or pathological paraffin-embedded, formalin-fixed tissues. The ER88 antibody specifically binds to antigens located in the nucleus of cell populations that express estrogen receptor in normal and abnormal tissues. This antibody is indicated as an aid in assessing patient response to hormonal therapy and as an aid in the prognosis and management of breast cancer patients. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

BioGenex ER88 antibodies have been optimally manufactured for use with BioGenex Super Sensitive MultiLink Detection Systems with or without BioGenex Automated Staining Systems.

STATEMENT OF HOW TECHNOLOGICAL CHARACTERISTICS COMPARED TO SUBSTANTIAL EQUIVALENT DEVICE:

A table is provided below comparing the similarities and differences between the BioGenex device and the predicate Dako Device (K993957) to detect estrogen receptors in normal and or pathological tissues.

	BioGenex (New device-K013148)	**Dako (Predicate device K993957)**
Clone	ER88	1D5
Antibody	Mouse monoclonal	Mouse monoclonal
Immunoglobulin Class	Mouse IgG1, Kappa	Mouse IgG1, Kappa
Intended Use	Is intended for laboratory use to qualitatively identify by light microscopy human estrogen receptor in normal	May be used in semi quantitative detection of human estrogen receptor in tissue sections of human

	and/or pathological paraffin-embedded, formalin-fixed tissues.	breast cancer by immunohistochemistry.
Indication	This antibody is indicated as an aid in assessing patient response to hormonal therapy and as an aid in the prognosis and management of breast cancer patients.	This antibody is indicated as an aid in assessing the likely hood of response to therapy as well as in prognosis and management of breast cancer patients.
Specificity	Human estrogen receptor in formalin-fixed paraffin embedded tissues.	Human estrogen receptor in formalin-fixed paraffin embedded tissues.
Total protein concentration:	10 mg/ml	10 mg/ml
Storage	2-8°C	2-8°C
Application	For manual and automated use	For manual and automated use

PERFORMANCE DATA:

1. **Specificity of Primary Antibody**

A total of 88 formalin-fixed and paraffin-embedded tissues covering a wide range of normal human tissue types were tested with the BioGenex ER88 antibody using BioGenex Super Sensitive HRP Detection System. In normal human tissues ER88 antibody demonstrated negative immunoreactivity with most tissues. However, positive immunoreactivity was observed with some normal tissues like the nuclei of acini and duct cells of mammary gland and myometrium and endometrium of uterus.

2. **Reproducibility**

(a) **Intra run (within-run) assay:** The reproducibility of staining was determined by staining 10 slides of the same tissues within a single run. All slides were stained by the same individual using the same set of reagents for each of the tissues tested. Evaluation of the results indicates no significant variation among the slides of the same tissue stained in the same run.

(b) **Inter run (run-to-run) assay:** The reproducibility between runs was determined by staining slides containing the same tissues over 10 different runs. Evaluation of the results indicates no significant variation among the slides of the same tissue stained in different runs.

(c) **Instrumental runs vs. manual runs:** Ten slides each were stained with the antibody manually and using BioGenex Automated Stainer for each of the tissues tested. Tissue blocks were selected to demonstrate reproducibility over a wide

range of reactivity scale. The prediluted form of ER88 antibody was used for this study along with BioGenex Super Sensitive MultiLink Detection System with DAB as the substrate. Evaluation of the results indicates no significant variation among the slides of the same tissue stained manually and in the automated process.

3. Sensitivity

Comparison between ER88 IHC and reference DCC assays. The study was designed to use independent clinical specimens to establish the performance characteristics of ER88 antibody staining and its concordance with the reference methodology, dextran-charcoal coated (DCC) assay. The DCC assay is a biochemical assay and has been considered the gold standard for ER assay. More recently, immunohistochemistry (IHC) has become a popular method for such testing (Kell, D et al. 1993, Goussard, 1998; Ferrero-Pous, M et al. 2001).

A total of 122 specimens were used in this study. All the specimens were selected according to the following criteria: 1) fomalin-fixed and paraffin-embedded tissue sections were available; 2) each tissue was initially assayed for ER by DCC. No other selection criteria were employed. The study was conducted using two different batches of clinical specimens to include approximately 50% positive and negative cases.

The first batch of 29 specimens was assayed for DCC in the laboratory of the late Dr. William McGuire at the University of Texas Health Science Center at San Antonio, Texas. The DCC results were scored as positive or negative using a cut-off value of ≥10 femtomoles/mg of protein. IHC staining of these slides was done in the laboratory of Dr. Louis P. Pertschuk in the Department of Pathology, King's County Hospital, State University of New York, Health Science Center, Brooklyn, New York using detection reagents provided by BioGenex.

The second batch of 93 specimens was assayed for DCC in the laboratory of Dr. William Fricke (Genesee Hospital, Rochester, NY). The DCC results were scored as positive or negative using a cut-off value of ≥10 femtomoles/mg of protein. The tissue blocks were provided to BioGenex laboratories for slide preparation and IHC staining using BioGenex detection reagents.

For both the studies, each resulting slide was read independently by two pathologists, who have no knowledge of any other laboratory or clinical data of the specimens. The scoring was based on percentage of cells with positive nuclear staining (Fitzgibbons PL, et al. 2000). Any trace of nuclear staining was counted as positive result (NIH Consensus Statement, 2000). The intensity of staining was not factored into the scoring system. A cut-off value of >10% of positive tumor cells was used to score a slide as positive or negative.

The overall binary concordance of ER88 IHC staining to ER DCC assay was 75% (92/122), with a 2-side 95% confidence interval of 68% - 83% ($p<0.0001$). This level of concordance indicated that ER88 IHC results and ER DCC results were similar. However, 25% of the results were discordant between these two methods. Reasons for discordance between hormone receptor IHC staining and hormone receptor DCC assays are well known (Kell, et al. 1993; Goussard, 1998; Ferrero-Poüs, et al. 2001). Since DCC requires specimen homogenization, the cellular localization of any detected receptor can not be determined. The receptor might be from either benign epithelium or tumor cells or both sources within the same tissue. With IHC, positive signals from only the tumor areas of the tissue are read by trained pathologists and signals from apparent normal areas from the same tissue are ignored. This would suggest that the IHC method is more specific than the DCC method.

4. Stability:

The objective of this study was to determine the expiration date of the device. The BioGenex ER88 Antibody was stored at 2-8°C continuous. Three lots of the device were tested after 24 months of storage following the standard in-house quality control testing procedures. Results of this study indicated that this device was stable for at least 24 months at 2-8°C.

Shipping stress studies were carried out on three lots of the device by continuous exposure to extreme temperature condition 45°C for 48 hours. Results of this study indicated that this device was stable after continuous 48 hour exposure at 45°C.

CONCLUSION:

The results indicate that BioGenex Monoclonal Anti-Estrogen Receptor (Clone ER88) is substantially equivalent to dextran-coated charcoal (DCC) technique and Dako estrogen receptor antibody (K993957).

BIBLIOGRAPHY:

Ferrero-Poüs M, Trassard, M, Le Doussal V, Hacène K, Tubiana-Hulin M, Spyratos, F. Comparison of enzyme immunoassay and immunohistochemical measurements of estrogen and progesterone receptors in breast cancer patients. Appl Immunohistochem & Mol Mor 2001;9:267-275.

Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, Ruby SG, O'Malley F, Simpson JF, Connolly JL, Hayes DF, Edge SB, Lichter A, Schnitt SJ. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med. 2000 Jul;124(7):966-78.

Kell D, Kamel O, Rouse R, Immunohistochemical analysis of breast carcinoma estrogen and progesterone receptors in paraffin embedded tissue. Appl Immunohistochem 1993;1(4):275-281.

Goussard J. Paraffin section immunocytochemistry and cytosol-based ligand-binding assays for ER and PR detection in breast cancer: the time has come for more objectivity. Cancer Lett 1998 Oct 23;132(1-2):61-66.

NIH Consensus Statement. Adjuvant Therapy for Breast Cancer, Volume 17, Number 4, November 1–3, 2000 National Institutes of Health, Office of the Director, pg. 8.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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FEB 2 8 2002

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Re: k013148
Trade/Device Name: BioGenex Mouse Anti-Estrogen Receptor Antibody (Clone ER88)
Regulation Number: 21 CFR 864.1860
Regulation Name: Immunohistological Reagents and Kits
Regulatory Class: Class II
Product Code: MXZ
Dated: December 20, 2001
Received: December 21, 2001

Dear Dr. Nanda:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number (if known): K013148

Device Name: BioGenex Mouse Anti-Estrogen Receptor Antibody (Clone ER88)

Indications for Use: The BioGenex Mouse Monoclonal Anti-Estrogen Receptor Antibody (Clone ER88) is an immunohistochemical (IHC) assay and is intended for laboratory use to qualitatively identify by light microscopy human estrogen receptor in normal and/or pathological paraffin-embedded, formalin-fixed tissues. The ER88 antibody specifically binds to antigens located in the nucleus of cell populations that express estrogen receptor in normal and abnormal tissues. This antibody is indicated as an aid in assessing patient response to hormonal therapy and as an aid in the prognosis and management of breast cancer patients. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

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(Please do not write below this line-continue on another page if needed)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over – The – Counter Use __
(Per 21 CFR 801. 109) (Optional format 1-2-96)

Sousan S. Altaie

(Division Sign-Off)
Division of Clinical Laboratory Devices

510(k) Number K013148